

## Executive summary

### Background

- ES1 There are two sources of vitamin D in the UK: exposure to sunlight (skin synthesis) and diet. Skin synthesis is the main source of vitamin D for most people.
- ES2 The two major forms of vitamin D are vitamin D<sub>3</sub> (cholecalciferol) and vitamin D<sub>2</sub> (ergocalciferol). Vitamin D<sub>3</sub> is synthesised in the skin of humans and animals by the action of sunlight containing ultraviolet B (UVB) radiation. Vitamin D<sub>2</sub> is the naturally occurring form found in plants and is synthesised by UVB exposure of ergosterol.
- ES3 Dietary sources of vitamin D in the UK are natural food sources, fortified foods and supplements. There are few naturally rich food sources of vitamin D. Dietary sources become essential when sunlight containing UVB light is limited (e.g., in winter) or exposure to sunlight containing UVB light is restricted.
- ES4 Dietary reference values (DRVs) for vitamin D, set by the Committee on Medical Aspects of Food Policy (COMA) in 1991 (DH, 1991), were based on prevention of rickets in children and osteomalacia in adults. A dietary intake of vitamin D was not considered necessary for individuals with adequate exposure to sunlight; therefore, a reference nutrient intake (RNI<sup>1</sup>) was not set for individuals aged 4-65 years '*living a normal lifestyle*'. RNIs were set only for certain population subgroups considered to be at risk of vitamin D deficiency: infants 0-6 months (8.5 µg/d); infants and children 7 months–3 years (7 µg/d); pregnant and breast-feeding women (10 µg/d), adults aged 65 or more years (10 µg/d), those with limited exposure to sunlight (e.g., confined indoors or wearing concealing clothing) and people of Asian ethnic origin (10 µg/d).
- ES5 The DRVs for vitamin D were reviewed and endorsed by COMA in 1998. Since then, however, studies have suggested a range of non-musculoskeletal health benefits of vitamin D. The data on vitamin D and health outcomes were considered by SACN in 2007. At that time, it was concluded that there was insufficient evidence to amend existing advice and that evidence on the relationship between vitamin D and non-musculoskeletal health was inconclusive.
- ES6 In 2010, SACN agreed to review the DRVs for vitamin D because a substantial amount of data had accumulated since 2007, including a comprehensive report in 2011 by the Institute of Medicine (IOM) in the US<sup>2</sup>, which provided an important resource for consideration of the evidence.

### Purpose and scope of current review

- ES7 The purpose of the current SACN review on vitamin D was to consider whether the DRVs for vitamin D set by COMA in 1991 are still appropriate in the context of current lifestyles (e.g., advice to stay out of the sun and to wear sunscreen). The key issues considered were:
- biochemical indicators of vitamin D status and the validity of the values used to assess risk of deficiency and excess;
  - association between vitamin D status and health outcomes at all life stages and the effects of biological modifiers;

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<sup>1</sup> The RNI represents the amount of a nutrient that is likely to meet the needs of 97.5% of the population.

<sup>2</sup> *Dietary Reference Intakes for Calcium and Vitamin D*.

- the contribution of cutaneous vitamin D synthesis to vitamin D status in the UK taking account of factors that modify skin exposure to sunlight; risks of skin damage and other adverse health outcomes associated with sunlight exposure;
- potential adverse effects of high vitamin D intakes; and
- relative contributions made by dietary vitamin D intake (from natural food sources, fortified foods and supplements) and cutaneous vitamin D synthesis, to the vitamin D status of the UK population.

ES8 In assessing the evidence on vitamin D and health outcomes, data from randomised controlled trials (RCTs), then prospective studies, were preferred in terms of informing the setting of DRVs when these were available; however, data from other study types were also considered (including case-control, cross-sectional studies and case reports).

### **Biology & metabolism**

ES9 Chapter 2 of the draft report provides an overview of the biology and metabolism of vitamin D.

#### **Biomarkers of exposure**

ES10 The active metabolite of vitamin D, 1,25(OH)<sub>2</sub>D, is not a suitable indicator of vitamin D exposure because it is homeostatically regulated and has a short half-life (< 4 hours). Serum 25(OH)D concentration is widely considered to be the best indicator of total vitamin D exposure (from the diet and sunlight) because it has a long half-life in the circulation (about 2-3 weeks) and is not subject to tight homeostatic control. As a marker of exposure to vitamin D, serum 25(OH)D concentration is influenced by those factors that affect dermal synthesis (including season, latitude, clothing, skin type).

ES11 There are limitations in using serum 25(OH)D concentration as a marker of vitamin D exposure since it has been observed to decrease in response to acute inflammation. It is therefore possible that low serum 25(OH)D concentrations (which have been observed in conditions such as cancer) may simply reflect an underlying inflammatory state. The relationship between exposure and serum 25(OH)D concentration may also be confounded by BMI and genetic variation.

ES12 Quantification of serum 25(OH)D concentration is influenced by the method used for its measurement. The main limitations associated with the methods used for measuring serum 25(OH)D concentration are accuracy and variability. Measurements can vary considerably (15-20%) depending on the type of assay used and across different concentration ranges. There is also lack of agreement between different laboratories using the same methods. This has implications for the interpretation of epidemiological studies and trials that have examined the relationship between serum 25(OH)D concentration and health outcomes.

#### **Photobiology**

ES13 The sun is the main source of ultraviolet radiation (UVR) which is categorised into three types according to wavelength: UVA (315-400 nm), UVB (280-315 nm) and UVC (100-280 nm). The UVR spectrum is modified on its path through the atmosphere by ozone, altitude, ground reflection (e.g., by sand or snow), air pollution, cloud cover and shade, time of day and season.

ES14 The amount of vitamin D synthesised in the skin depends on skin exposure to UVB radiation and efficiency of cutaneous synthesis. There is a well observed seasonal cycle in serum 25(OH)D concentrations in the UK. During winter, the small amount of UVB in sunlight is insufficient to

initiate synthesis of any biologically relevant quantities of vitamin D. Sunlight-induced vitamin D synthesis in white-skinned populations becomes effective from March with maximum concentrations observed in September after a summer of exposure. Serum 25(OH)D concentration decreases from October onwards throughout the winter months.

ES15 The first step in endogenous vitamin D synthesis is the conversion by solar UVB radiation of 7-dehydrocholesterol (7DHC) in the skin to previtamin D. The amount of 7DHC present in the skin decreases with increasing age but the age at which this becomes a limiting factor if there is ample exposure to sunlight is unclear.

ES16 The pigment melanin absorbs some of the UVB radiation which would otherwise be absorbed by 7DHC. This means that if the absolute dose of UVB radiation is the same as that given to a person with white skin then people with darker skin will synthesise less vitamin D. However, darker skin has the same capacity to synthesise vitamin D if the dose of radiation is adjusted for the protective effect of melanin.

### **Vitamin D and health outcomes**

ES17 Vitamin D has been associated with a number of musculoskeletal and non-musculoskeletal health outcomes.

#### *Musculoskeletal health outcomes*

ES18 Evidence on vitamin D and musculoskeletal health outcomes was considered by life stage since different musculoskeletal health measures are appropriate for specific age groups. Rickets was considered in infants and children; osteomalacia and bone health indices (BMC, BMD, biochemical markers of bone turnover) were considered across all age groups; muscle strength and function was considered in all adults; fracture prevention and risk of falls were considered in adults > 50 y.

ES19 Evidence on rickets is derived mainly from observational studies and therefore subject to confounding. An important limitation in these studies was that most did not measure calcium intake which is a potential confounding factor in studies on rickets. There was great variation in the serum 25(OH)D concentration at which rickets was present but concentrations were < 25 nmol/L in the majority of studies considered. This suggests that the risk of rickets is increased at serum 25(OH)D concentration < 25 nmol/L; this concentration is, however, not diagnostic of the disease. The concentration below which there is increased risk of rickets specifically due to vitamin D is uncertain.

ES20 Evidence on vitamin D and osteomalacia is limited and is drawn mainly from case reports. There is no clear serum 25(OH)D threshold concentration below which risk of osteomalacia is increased but concentrations were < 20 nmol/L in all the studies considered.

ES21 Findings from studies that considered the relationship between vitamin D and bone health indices (BMC/BMD/biochemical markers of bone turnover) varied by life stage. Evidence was suggestive of a positive association between maternal 25(OH)D concentration during pregnancy and bone health indices in the fetus/newborn and of beneficial effects of vitamin D supplementation on bone health indices at some skeletal sites in adults aged > 50 years. Evidence on vitamin D and bone health indices in infants, children and adolescents and adults < 50 years was either inconsistent or insufficient to draw conclusions.

ES22 Although cohort studies suggest an association between increased serum 25(OH)D concentration

and decreased fracture risk, evidence from RCTs show that vitamin D supplements appear to have no effect on fracture risk in older men and women.

ES23 Evidence on vitamin D and falls is mixed but overall is suggestive of a beneficial effect of vitamin D supplementation in reducing fall risk in community dwelling adults > 50 years with baseline serum 25(OH)D concentrations across a range of values. One study reported an increase in fall risk with vitamin D supplementation (12,500 µg/500,000 IU); however, the dose was very high and administered annually which may produce different effects from daily supplementation.

ES24 Evidence from RCTs suggest that vitamin D supplementation may improve muscle strength and function in adults < 50 years with mean serum 25(OH)D concentration < 30 nmol/L. In adults > 50 y, the evidence is mixed but, overall, suggestive of beneficial effects on muscle strength and function with mean baseline serum 25(OH)D concentrations across a range of values.

#### *Non-musculoskeletal health outcomes*

ES25 A range of non-musculoskeletal health outcomes were considered: oral health, reproductive health (on maternal & newborn outcomes) all-cause mortality, cancer, cardiovascular disease, hypertension, infectious disease (TB, influenza, respiratory tract infection, obstructive pulmonary disease), autoimmune disease (asthma, atopic disorders, multiple sclerosis, type 1 diabetes, inflammatory bowel disease, rheumatoid arthritis), age-related macular degeneration and neuropsychological functioning (cognitive function, dementia, autism, depression, schizophrenia).

ES26 Evidence for the proposed benefits of vitamin D on non-musculoskeletal health outcomes is drawn mainly from observational studies so findings might be due to reverse causality (i.e., low 25(OH)D concentration is a consequence of the illness rather than the cause) or confounding by other factors associated with a specific health outcome. There is limited RCT evidence for some non-musculoskeletal health outcomes and the findings are inconsistent.

ES27 Overall, there was insufficient evidence on vitamin D and non-musculoskeletal health outcomes to inform the setting of DRVs for vitamin D.

#### **Selection of health outcomes to be used as the basis for setting DRVs for vitamin D**

ES28 Musculoskeletal health outcomes (based on evidence relating to rickets, osteomalacia, falls and muscle strength and function) were selected as the basis for setting the DRVs for vitamin D.

ES29 There was wide variability in the mean and individual serum 25(OH)D concentrations associated with increased risk of poor musculoskeletal health; however, risk appears to increase at concentrations below 20-30 nmol/L. Interpretation of the data is complicated by the fact that measurement of serum 25(OH)D concentration is affected by inter-assay differences. Since various assay methods were used in the studies considered there are difficulties in making comparisons between studies on serum 25(OH)D concentrations associated with risk.

ES30 The number of uncertainties in the data makes it difficult to identify a specific serum 25(OH)D threshold concentration between 20-30 nmol/L associated with increased risk of poor musculoskeletal health. The current threshold of 25 nmol/L used to define the concentration below which risk of vitamin D deficiency is considered to increase (DH, 1998) is therefore retained. This threshold is not diagnostic of disease but indicative of increased risk of poor musculoskeletal health.

#### **Potential adverse effects of high exposures to vitamin D**

ES31 The endpoint used to assess the effects of high exposure to vitamin D was hypercalcaemia since adverse effects unrelated to elevated calcium have not been reliably documented. The Tolerable Upper Intake Levels (UL<sup>3</sup>) for vitamin D recommended by the European Food Safety Authority (EFSA) are 100 µg/d (4000 IU) for adults and children aged 11-17 y, 50 µg/d (2000 IU) for children aged 1-10 y and 25 µg/d (1000 IU) for infants. The TULs were considered appropriate by the COT<sup>4</sup>. The UL may not apply to individuals with some health conditions such as normocalcaemic hyperparathyroidism and granulomatous conditions (including sarcoidosis and tuberculosis) which predispose to hypercalcaemia or to those with genetic predispositions such as idiopathic infantile hypercalcaemia.

ES32 Case reports of vitamin D toxicity are associated with serum 25(OH)D concentrations > 300 nmol/L and more usually 600-1000 nmol/L. In adults, a single dose of 7500 µg (300,000 IU) vitamin D every 3 months or less would not be expected to result in serum 25(OH)D concentrations > 300 nmol/L but the risk of this occurring in some individuals would be higher with increasing doses. Vitamin D doses of 15000 µg (600,000 IU) would be expected to cause hypercalcaemia and potentially cause adverse effects in infants.

#### **Vitamin D intakes and serum 25(OH)D concentrations in the UK population**

ES33 Nationally representative data on vitamin D intakes and serum/plasma 25(OH)D concentrations of the general population in the UK were drawn from the: National Diet and Nutrition Survey (NDNS) rolling programme of adults and children aged 18 months upwards (2008/09-2011/12); NDNS Scotland report (2008/09-2011/12), 2011 UK Diet and Nutrition Survey of Infants and Young Children (DNSIYC); Health Survey for England (HSE); and Scottish Health Survey (SHS). Data on low income population groups (aged 2+ years; 2003-5) were drawn from the Low income Diet and Nutrition Survey (LIDNS). Data on pregnant women were obtained from UK based cohort studies<sup>5</sup>.

ES34 Blood collection within the NDNS rolling programme, LIDNS, HSE and SHS is spread evenly across the year. In the DNSIYC blood samples were collected between the months of February and August. In the consideration of these data, it is important to be aware that measurements of serum 25(OH)D concentration from different surveys may not be comparable since they can vary considerably depending on the type of assay used. There is also a lack of agreement between different laboratories using the same methods.

ES35 Chapter 8 of the draft report provides information about dietary sources of vitamin D and vitamin D intakes in the UK. Together with the tables in Appendix 2, this chapter also provides detailed information about serum/plasma 25(OH)D concentrations in particular population groups and how these vary according to ethnicity, season and region; it includes data on the proportion of various groups with 25(OH)D concentrations below 25nmol/L. The information is summarised in Chapter 10.

#### **Review of DRVs**

ES36 The DRVs describe the distribution of requirements in a population and comprise 3 estimates: the *Estimated Average Requirement (EAR)*, half of a group in a population will need more than this

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<sup>3</sup>UL - the maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans. The UL is not a recommended level of intake. It is an estimate of the highest level of intake which carries no appreciable risk of adverse health effects.

<sup>4</sup> Committee on Toxicity of Chemicals in Foods, Consumer Products and the Environment.

<sup>5</sup> Nationally representative data are not available for pregnant women.

amount and half will need less; the *Reference Nutrient Intake (RNI)*, the amount that will meet the needs of 97.5% of the population; and the *Lower Reference Nutrient Intake (LRNI)*, the intakes which will meet the needs of only 2.5% of the population.

- ES37 Previously in the UK, the DRVs for vitamin D set by COMA were only for population groups at high risk of deficiency (DH, 1991). It was assumed that, for most people, the amount of vitamin D produced by exposure to sunlight containing UVB would be adequate for achieving serum 25(OH)D concentrations above  $\geq 25$  nmol/L during winter. It is now known that this is not the case.
- ES38 In the current review, the health outcome identified as the basis for setting DRVs for vitamin D was musculoskeletal health (based on rickets, osteomalacia, falls and muscle strength). Although the data were not sufficient to establish a distribution of serum 25(OH)D concentrations or a clear threshold serum 25(OH)D concentration to support musculoskeletal health outcomes, the evidence overall suggests that the risk of poor musculoskeletal health is increased at serum 25(OH)D concentrations  $< 25$  nmol/L.
- ES39 A serum 25(OH)D concentration of 25 nmol/L was therefore selected, on a precautionary basis, as the target concentration to protect all individuals from poor musculoskeletal health. This concentration was considered to be a '*population protective level*'; i.e., the concentration that 97.5% of individuals in the UK should be above, throughout the year, in terms of protecting musculoskeletal health.
- ES40 The next step in estimating DRVs for vitamin D was translation of the serum 25(OH)D concentration of 25 nmol/L into a dietary intake value that represents the RNI for vitamin D; i.e., the average daily vitamin D intake that would be sufficient to maintain serum 25(OH)D concentration  $\geq 25$  nmol/L in 97.5% of individuals in the UK. The average vitamin D intake refers to the mean or average intake over the long term and takes account of day to day variations in vitamin D intake.
- ES41 Sun exposure is the major source of vitamin D during the summer months for the majority of people in the UK. It was not possible to quantify the sunlight exposure required in the summer months to maintain a winter serum 25(OH)D concentration of at least 25 nmol/L because of the number of factors that affect endogenous vitamin D synthesis, storage and utilisation.
- ES42 The RNI was estimated by modelling data from individual RCTs in adults (men & women, 20-40 y and 64+ y) and adolescent girls (11 y). The RCTs had been conducted in winter so that dermal production of vitamin D was minimal.
- ES43 The modelling exercise indicated that the estimated average daily vitamin D intake required to maintain serum 25(OH)D concentration  $\geq 25$  nmol/L in winter by 97.5% of the population is 12  $\mu\text{g}$  based on serum 25(OH)D analysis by LC-tandem MS or 9  $\mu\text{g}/\text{d}$  based on analysis of the same sera by immunoassay. Since the target threshold serum 25(OH)D concentration of 25 nmol/L was based on studies which had used a range of different assays to measure serum 25(OH)D concentration, the RNI was set between these 2 estimates, at 10  $\mu\text{g}/\text{d}$ .
- ES44 Data were not available to allow direct determination of the vitamin D intake required to reach serum 25(OH)D concentrations  $\geq 25$  nmol/L in infants and children aged 0-10 y. However evidence suggests that age does not affect the response of serum 25(OH)D concentration to vitamin D intake; data from the modelling exercise were therefore extrapolated to younger age groups.
- ES45 An RNI of 10  $\mu\text{g}/\text{d}$  is proposed for the UK general population aged 11-64+ y. The RNI assumes

minimal sunshine exposure because the studies used to derive this figure were conducted in winter. This is the amount needed to achieve a serum 25(OH)D concentration  $\geq 25$  nmol/L during winter in 97.5% of the population.

ES46 Although most people would be expected to synthesise vitamin D during summer, serum 25(OH)D concentrations  $< 25$  nmol/L have been observed in a proportion of some population groups in the UK during the summer months. Since it is not possible to identify these individuals, it is proposed that the RNI is applicable throughout the year. This is a precautionary approach to protect the most vulnerable groups in the population and to take account of variable exposure to sunshine and diet. This approach ensures coverage of 97.5% of the population throughout the year.

ES47 The RNI of 10  $\mu\text{g}/\text{d}$  proposed for the general UK population includes pregnant and lactating women.

ES48 Since data are not available to relate serum 25(OH)D concentration in the infant clearly to current or long term health, *Safe Intakes*<sup>6</sup> rather than RNIs are proposed for ages 0-3 years. Safe Intakes are based on a precautionary approach and reflect the insecurities of the data. A Safe Intake of 8.5-10  $\mu\text{g}/\text{d}$ , based on concentrations of vitamin D in infant formula, is proposed for children age 0-11 months. A Safe Intake of 10  $\mu\text{g}/\text{d}$ , based on the RNI for the UK population, is proposed for infants and children aged 1-3 years.

ES49 There is currently no vitamin D RNI for exclusively breast fed infants because it was previously assumed that maternal vitamin D supplementation during pregnancy and breast milk would provide the infant with adequate vitamin D for the period of exclusive breast feeding. The few available data suggest that it is unlikely that an exclusively breast fed infant in the UK would maintain serum 25(OH)D concentration  $\geq 25$  nmol/L for 6 months. Therefore the Safe Intakes proposed for non-breast fed infants are also proposed for exclusively breast fed infants (from birth).

ES50 For ages 4–10 years, the RNI of 10  $\mu\text{g}/\text{d}$  proposed for the UK population (11-64 y) is considered appropriate.

ES51 Population groups considered to be at risk of having serum 25(OH)D concentrations  $< 25$  nmol/L include people from ethnic groups with dark skin. The role of skin colour, however, is complicated by behaviours that could also affect serum 25(OH)D concentration (e.g., wearing clothes that cover the skin when outdoors; sun avoidance). Other population groups at risk of having individuals with serum 25(OH)D concentrations  $< 25$  nmol/L include frail and institutionalised people and those not spending substantial time outdoors. An increment added to the RNI was not considered necessary for these '*at risk*' population groups because the recommendation that the RNI is applicable throughout the year is to take account of individuals with minimal sunshine exposure, including those most at risk.

ES52 There is evidence suggesting that obese people are also at risk of low serum 25(OH)D concentrations; however, the data are insufficient to support a different recommendation from that of the general UK population.

ES53 Although achievement of the proposed RNI by the UK population would lead to an increase in mean/median vitamin D intakes of the UK population, it is unlikely that this would lead to vitamin D intakes at the upper end of the distribution reaching levels that might pose a risk of adverse effects.

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<sup>6</sup> COMA (DH, 1991) set a '*Safe Intake*' for some nutrients if there were insufficient reliable data to set DRVs. They are set on grounds of prudence and are '*judged to be a level or range of intake at which there is no risk of deficiency, and below a level of where there is a risk of undesirable effects*' (DH, 1991).

## Recommendations

ES54 Serum 25(OH)D concentration is an indicator of exposure to vitamin D (i.e., from the diet and skin synthesis). In order to protect musculoskeletal health, it is recommended that the serum 25(OH)D concentration of individuals in the UK should not fall below 25 nmol/L at any time of the year.

ES55 In the UK, population groups at increased risk of having a serum 25(OH)D concentration < 25 nmol/L are those with minimal sunshine exposure as a result of not spending substantial time outdoors (e.g., frail and institutionalised people) or due to the habitual wearing of clothing that covers most of the skin while outdoors.

ES56 It is not possible to make a recommendation regarding the amount of sunlight exposure that would be required during the summer to maintain serum 25(OH)D concentration  $\geq$  25 nmol/L in 97.5% of the population during winter because of the number of factors that affect endogenous vitamin D production.

ES57 A Reference Nutrient Intake (RNI) for vitamin D of 10  $\mu\text{g}/\text{d}$  is therefore proposed for the UK population aged 4 years and over. This is the amount needed for 97.5% of the population to maintain a serum 25(OH)D concentration of 25 nmol/L when UVB sunshine exposure is minimal.

ES58 The RNI of 10  $\mu\text{g}/\text{d}$  proposed for the whole UK population includes individuals from minority ethnic groups with darker skin.

ES59 It is proposed that the RNI is applicable throughout the year, as a precautionary measure, to cover population groups in the UK identified to be at risk of minimal sunshine exposure as well as unidentified individuals in the population with minimal sunshine exposure who would be at risk of 25(OH)D concentrations < 25 nmol/L in summer.

ES60 Data are insufficient to set RNIs for infants and children aged 0-3 years. As a precaution, a 'Safe Intake' of vitamin D is therefore proposed for these ages: in the range 8.5-10  $\mu\text{g}/\text{d}$  for ages 0 to < 1 year (including exclusively breast fed infants); and 10  $\mu\text{g}/\text{d}$  for ages 1 to < 4 years.

ES61 Since it is difficult to achieve the RNI/Safe Intake from natural food sources alone, it is recommended that consideration is given to strategies for the UK population to achieve the RNI of 10  $\mu\text{g}/\text{d}$  for those aged 4 years and older and for younger children to achieve a Safe Intake in the range 8.5-10  $\mu\text{g}/\text{d}$  at ages 0 to < 1 year and 10  $\mu\text{g}/\text{d}$  at ages 1 to < 4 years.